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A Model of Tuberculosis Transmission and Intervention Strategies in an Urban Residential Area

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Abstract

The model herein aims to explore the dynamics of the spread of tuberculosis (TB) in an informal settlement or township. The population is divided into households of various sizes and also based on commuting status. The model dynamics distinguishes between three distinct social patterns: the exposure of commuters during travel, random diurnal interaction and familial exposure at night. Following the general SLIR models, the population is further segmented into susceptible (S), exposed/latently infected (L), active/infectious (I), and recovered (R) individuals. During the daytime, commuters travel on public transport, while non-commuters randomly interact in the community to mimic chance encounters with infectious persons. At night, each family interacts and sleeps together in the home. The risk of exposure to TB is based on the proximity, duration, and frequency of encounters with infectious persons. The model is applied to a hypothetical population to explore the effects of different intervention strategies including vaccination, wearing of masks or scarves during the commute, prophylactic treatment of latent infections and more effective case-finding and treatment. The most important findings of the model are: (1) members of larger families are responsible for more disease transmissions than those from smaller families, (2) daily commutes on public transport provide ideal conditions for transmission of the disease, (3) improved diagnosis and treatment has the greatest impact on the spread of the disease, and (4) detecting TB at the first clinic visit, when patients are still smear negative, is key.

1. Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, is one of the world's leading causes of infectious mortality. The World Health Organization (2009) reported 9.3 million incident cases and 1.8 million TB-related deaths worldwide in 2007 alone. Nearly 80% of both incident cases and deaths were in twenty-two "high-burden" countries, mostly located in Sub-Saharan Africa and Southeast Asia, where the problem is exacerbated by high rates of co-infection with HIV (WHO, 2009). South Africa has been particularly burdened by the epidemic, with the world's highest prevalence of HIV in incident TB cases (73%) and the second-highest prevalence of TB overall (692 per 100,000) as of 2007 (WHO, 2009). These rates are appreciably higher in the densely-populated, underdeveloped townships surrounding South Africa's largest cities. In a survey of 762 randomly selected adults living mostly in shacks in a South African township, Wood et al. (2007) found a sputum smear-positive TB prevalence of 4,400/100,000 for HIV-positive

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individuals and 527/100,000 for HIV-negative individuals. The emergence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains, accounting for approximately 5% of cases (WHO, 2009), is an additional complication, though they will not be considered in this model.

Most individuals infected with TB develop an asymptomatic latent infection. Over the course of a lifetime, approximately 5% to 10% of latent infections progress to active TB in otherwise healthy individuals, either by endogenous reactivation of the existing infection or exogenous reinfection with a new strain. The probability to progress to active TB is markedly higher for people who are infected by HIV (up to 10% per year). A mathematical model by Feng *et al.* (2000) indicated that exogenous reinfection of latent individuals is a major driving force in TB epidemics, and that treatment strategies aiming to reduce R_0 (the number of secondary infections caused by an infectious person during their infectious period) below unity may be insufficient to eradicate TB.

Interactions in mass transit systems, where ventilation is poor and close contact is prolonged, may share the blame for the resurgence of TB in recent years (Aparicio *et al.*, 2000; Feng *et a*l., 2000). Horna-Campos *et al.*, (2007) found traveling in minibuses to be a risk factor for pulmonary TB in Lima, Peru. On the other hand, transmission of TB during air travel has been deemed unlikely on short flights (Moore *et al.*, 1996), most probably due to better ventilation in aircraft. Nonetheless, transmissions during air travel have been confirmed on longer flights (Kolata, 1995), and has led to at least one high-profile scare in recent years (Altman, 2007). These reports suggest that transmission strongly depends on prolonged and repeated exposure to be successful. The population in a typical township relies heavily on public transportation (minibus taxi's, buses and trains) for transportation outside the boundaries of the township. The townships, then, provide an important case study for the effects of close-contact social interactions, including public transport, on the epidemiology of TB in a population where the disease is highly prevalent.

A large number of models of TB are based on mass-action principles and assume a homogeneously mixed population (Blower and Gerberding, 1998; Blower *et al.*, 1995; Blower *et al.*, 1996; Castillo-Chavez and Feng, 1997; Feng *et al.*, 2000; Vynnycky and Fine, 1997; among others). Schinazi (2003) made an intuitive argument for the importance of spatial effects on individuals when exogenous reinfection is under consideration. Latently infected individuals are much more likely to be reinfected by prolonged contact with an infectious neighbor when movement is highly restricted (to the stationary limit, in the Schinazi case) than when the population is well-mixed and reinfection opportunities are random and fleeting.

Clustered populations have also been modeled in the analysis of the spread of TB. Schinazi (2002) explored epidemiological dynamics in a socially clustered population, and showed that the likelihood of an epidemic depends on the infection rate from outside the cluster as well as the cluster size being large enough. Belhadji and Lanchier (2006) used a similar model to determine that epidemics are highly unlikely in a "cluster recovery process" population, where there is a good tracking system in place as soon as an infection is identified. Other models cluster individuals into households (Ball and Lyne, 2002; Ball *et al.*, 2004). A network-based model constructed by Keeling (2005) predicted an infection would persist in a clustered population much longer than in a mass-action model. Beyers *et al.* (1996), who studied the geographic distribution of TB infections in two Western Cape (South African) suburbs and found that infection persisted in certain houses, also showed empirical evidence for the importance of spatial effects. While human contact is more complex than either of these extremes, a robust model ought to include elements of each.

An individual member of a community can be assigned to a household cluster, assuming that each member of the household has the same risk of infection from outside the cluster. As different members of the household have different routines, this approach might not capture the true dynamics of infections from outside the cluster. Assigning individuals to social clusters (i.e. a group of people, not limited to their household, with which they have regular contact), would move toward a better approximation of reality. However, this approach assumes the same risk of infection from a household member as from a neighbor or colleague. Here we propose the assignment of individuals to different clusters during different times of the day. Household members are grouped together in one cluster during the night, while certain members of households are all grouped together into a cluster of commuters during the day. Commuters are further clustered daily into smaller groups that are in the same vehicle during the commute. The movement between the clusters creates a connection and opportunity for transmission between clusters, higher than would be considered in a single cluster model. Therefore, the model can be considered a hybrid of a clustered population (households at night, commuters during the day) and a well mixed population (non-commuters during the day, and commuters that are clustered into different vehicles daily).

The TB epidemic is clearly a very complex problem; which is not being contained by the current control measures. The many facets of the epidemic are universal in some cases (e.g. emergence of resistance), but region specific in others (e.g. available infrastructure and routes of transmission). Therefore, effective worldwide disease management will require a deeper understanding of the dynamics of the disease on a community basis. To this end we present a model of the spread of TB in an urban community, and explore the outcomes of different intervention strategies. We present this model (applied to different communities) as a tool to help identify the persons most likely to transmit TB and the interventions which are most likely to reduce the number of infected people in that setting.

2. Mathematical Model

2.1 The Community

This model considers a hypothetical urban community. The community under consideration is assumed to be a district of a larger township, and therefore, despite overall population changes in the township it can be assumed that the population in this established geographical area remains constant.

The township population consists of four states: susceptible (S), latently infected (L), infectious (I), and recovered (R) persons. For TB the infectious population is taken to include all individuals with active disease that are producing infectious quanta. Latently infected individuals are infected by the bacteria, but do not have active disease, and are therefore not contagious. Recovered individuals had active disease in the past, but were able to contain the infection. Susceptible individuals have not had any infection yet.

The community population is taken to consist of 10,000 families. This population is grouped into families of size $1 \leq k \leq 10$. Here, fhe families are given a normal distribution in size $m_k \in \{500,700,900,1100,1500,1500,1300,1000,900,600\}$. Application of this model to other communities will then require the size distribution in households to be adjusted. For example, there are 600 families of size 10. The average family size is 5.67; therefore, the initial population is 56,700. Individuals are probabilistically assigned a commuting status and infection status independent of one another. The standard employment rate, ε, is used as an estimate for the fraction of the community that commutes. The probabilities to be initially assigned to the classes S, L, I, and R are $\{0.27, 0.67, 0.01, 0.05\}$. This infectious fraction is taken from Wood *et al.*, (2007) who studied a township community with a high TB

notification rate, a high HIV rate, and a well-functioning TB control program. The prevalence of latent infections in this population is expected to be higher than the 33% value for the world population, but not as high as the 89% found in gold-mine workers in South Africa (Hanifa *et al.* 2009).

Again, the number of homes is relatively fixed and families will move in/out keeping the population constant. Migration into and out of the community is modeled by 1) replenishing the population number daily (according to the initial infection ratios) if the total population drops below the starting population, and 2) people move out of the township if the starting population is exceeded.

2.2 Assigning a structure to the population

The population is structured according to family size and commuter-status to describe three different social activities, each of which involves unique transmission dynamics:

household - socializing and sleeping in the home at night.

commuting – commuters travel to and from a site outside the township, whilst non-commuters interact casually (random walk) in the township.

Each family of size k is given a second index j to distinguish it from other families of the same size. The members of a family (k, j) are distributed among the four infection classes as follows:

$\mathbf{F}_{kj} = (S_{kj}, L_{kj}, I_{kj}, R_{kj})^T$, where the superscript T refers to a transposed vector.

At the start of a simulation, $S_{kj} + L_{kj} + I_{kj} + R_{kj} = k$, but over the course of the simulation the size of the family may change due to births or deaths. However, the members are still identified by the original indices, even in the case of deaths ($S_{kj} + L_{kj} + I_{kj} + R_{kj} < k$) or births ($S_{kj} + L_{kj} + I_{kj} + R_{kj} > k$). The family members are further distinguished from each other on the basis of their commuting:

$$\mathbf{F}_{kj}=\lfloor W_{kj}, U_{kj}\rfloor \text{ where } W_{kj}=\left(S_{kj}^{W}, L_{kj}^{W}, I_{kj}^{W}, R_{kj}^{W}\right)^{T} \text{ and } U_{kj}=\left(S_{kj}^{U}, L_{kj}^{U}, I_{kj}^{U}, R_{kj}^{U}\right)^{T}.$$

W_{kj} and U_{kj} denote commuters who travel daily to and from a site outside the township, and non-commuters who spend their day in the township, respectively. If we omit the subscripts, then it implies summing over all families; thus W and U are the total number of commuters and non-commuters in the township. Likewise S^W is the total number of susceptible persons who commute and S^U is the total number of non-commuting susceptible persons.

2.3 Transmission dynamics

A flowchart for the dynamics of each class of infection (S, L, I, and R) is shown in Figure 1. The source term in the overall population balance is the per-capita birth rate $\prod$. The sink terms are the death rates from TB and other causes, μ_{TB} and μ. A newly infected susceptible or recovered person progresses immediately to active TB with probability ρ and to latency with probability $(1 - \rho)$. Latent and recovered individuals harbor partial immunity to new infections, denoted by the constant σ. The analogous factor for immunity due to immunization of susceptible individuals is σ_v. Latent infections may progress to active TB by exogenous re-infection or endogenous reactivation of the existing infection (with rate ω), or may be contained by chemoprophylaxis with rate ψ. Infectious individuals are cured at rate c without treatment or rate $\varphi f\delta$ with treatment, where φ is the inverse of the average duration of infectiousness prior to diagnosis, f is the case-finding proportion, and δ is the average treatment success rate. The transmission rate β given in Figure 1 is an aggregate of

the differing transmission rates for various types of social interaction. The values of the variables listed above are given in Tables 2 and 3; an explanation of their estimation is given in the Appendix.

The following simplifying assumptions were made:

- Only pulmonary tuberculosis is considered.
- All strains are equally infectious, equally sensitive to treatment, and all have the same mortality rate.
- No explicit distinction is made between HIV-positive and HIV-negative individuals. Parameters such as the delay time before diagnosis and the case-finding rate consist of a weighted average of the respective values for the HIV-positive and negative subpopulations.
- The area of the township remains constant throughout the simulation.
- We have assumed lower prevalence rates outside the community, and therefore that the risk of exposure at outside sites is negligible.
- Individuals are not grouped based on age. Age-related differences, such as a reduction in infections due to children who do not have pulmonary TB, are not incorporated into the model.
- The progression rate from the latent to the infected state is assumed to be uniform to keep the number of parameters down and to instead give an average expected outcome for the population. This model does not include a non-linear distributed latent period (Aparicio *et al.*, 2002; Ziv *et al.*, 2000).

Note: If a distinction were made between HIV-positive and HIV-negative individuals, one would add another population group with different values of ρ, ω, μ_{TB} and *c* for the immune-compromised HIV-positive individuals. Although very important, the explicit dynamics of co-infection with HIV and TB is outside the scope of this model. Instead, the effect is included implicitly by weighting parameters.

2.4 Transmission depends on type of activity

The daily schedule used in this model is shown in Table 1. During each activity, people can become infected based on the activity and the number of infectious people in the vicinity. Births, deaths, endogenous reactivation, and therapeutics are assigned randomly, once per 12 hour period, on a per-capita basis. In the following section, the probabilities of transmission are derived for the three different activities.

Transmission rates depend on the environment. The rates are different for spatially confined settings, such as family socializing and the taxi commute, and unconfined interactions, such as random walk in the township. Beggs, *et al.* (2003) reviewed three analytical models of epidemiology in confined spaces and concluded that the model of Gammaitoni and Nucci (1997) was best suited to modeling TB transmission. The strengths of the model are (1) its recognition that the probability of exposure has a Poisson distribution in time, and (2) the ability to fix an initial concentration of infectious particles in the air at the beginning of an occupancy period. Gammaitoni and Nucci's model is based on the following set of equations,

$$\frac{dS}{dt} = -\frac{r}{V} nS$$
$$\frac{dn}{dt} = -Nn + I\gamma$$

where S and I are the number of susceptible and infectious people in the space, respectively, r is the pulmonary respiration rate, V is the volume of the space, n is the number of infectious quanta in the air, N is the ventilation rate in air changes (AC) per minute, and γ is the quanta generation rate per person. A quantum is defined by Wells (1955) as a certain number of infectious droplet nuclei, such that a person inhaling one quantum will be infected with probability $1-1/e$. The solution of these two differential equations is trivial. The number of infectious quanta in the air at time t and initial concentration n_0 is

$$n(t)=\frac{I\gamma}{N}+\left(n_0-\frac{I\gamma}{N}\right)\exp[-Nt].$$

For $n_0 = 0$, Beggs et al. gives the probability to be infected in the interval $0 \le t$,

$$P(t)=1-\exp\left[-\frac{rI\gamma}{V}\left(\frac{Nt+\exp[-Nt]-1}{N^2}\right)\right]. \quad (1)$$

The probability $P(t)$ is a Poisson distribution that can be applied to the activities listed in Table 1. Only the parameters in eq.(1) need to be adjusted to account for the specifics of an activity. The parameters V, N, and t are listed for the different activities in Table 2.

2.5 Transmission for households at night

Starting with the first activity listed in Table 1, the definition set for 'sleep/interact at home' is W_{kj} and U_{kj}. The operator L_H maps the definition set F^n_{kj} at time n (denoted as a superscript) onto itself at time $n + 1$:

$$L_H F^n_{kj}=\begin{bmatrix} (1-\sigma_v P_{Inf})-P_D+P_B & P_B & P_B & P_B \\ (1-p)\sigma_v P_{Inf} & 1-\sigma P_{Inf}-P_\psi-P_\varpi-P_D & 0 & (1-p)\sigma P_{Inf} \\ p\sigma_v P_{Inf} & P_\varpi+\sigma p P_{Inf} & 1-P_\phi-P_C-P_{DI} & p\sigma P_{Inf} \\ 0 & P_\psi & P_\phi+P_C & 1-\sigma P_{Inf}-P_D \end{bmatrix} \begin{bmatrix} S^W_{k,j} & S^U_{k,j} \\ L^W_{k,j} & L^U_{k,j} \\ I^W_{k,j} & I^U_{k,j} \\ R^W_{k,j} & R^U_{k,j} \end{bmatrix} = F^{n+1}_{kj} \quad (2)$$

Each one of the terms in L_H is a probability, described below, operator is applied once for every day. The death rate from non-TB causes is μ = 1340/100,000 per year (Anderson and Philips, 2006). Thus the probability to die of non-TB related causes over a 12 hr period (the time for this activity) is expressed in years as $t_{activity} = 1/(2 \times 365)$ is written as follows:

$$P_D=\mu \times t_{activity}=(1340/100,000) \times \frac{1}{2 \times 365}.$$

The death rate for people with active TB, μ_{TB}, is higher than the rest of the population (derived from non-TB and TB related mortality statistics by Anderson and Philips, 2006, and WHO, 2009). Thus

$$P^{TB}_D=\mu_{TB} \times t_{activity}=0.333 \times \frac{1}{2 \times 365}.$$

The birth rate is 2,930 per 100,000 per year (van Rie 1999) and it is converted to a probability over a 12 hr period.

$$P_B=\pi \times t_{activity}=0.0293 \times \frac{1}{2 \times 365}$$

Note that P_B appears in the top row across all columns, this implies that births contribute to the susceptible worker and non-worker pools. Without further complicating the model, we assume that $P_B \times \left(S_{kj}^U+L_{kj}^U+I_{kj}^U+R_{kj}^U\right)$ is the probability for a birth adding to S_{kj}^U, but $P_B \times \left(S_{kj}^W+L_{kj}^W+I_{kj}^W+R_{kj}^W\right)$ is the probability that a non-commuting person enters the commuting population. It is unlikely that all new entries to the commuting population are susceptible persons, but the formulation is simplified.

To determine the probability for infection during the time a family F_{kj} spends together for the 12 hr evening/night period, eq. (1) is modified as follows:

$$P_{Inf}=1-\exp\left[-\frac{r(I_{kj})\gamma}{V}\left(\frac{12N+\exp[-12N]-1}{N^2}\right)\right]. \quad (3)$$

The probability differs from family to family, because the number of infected persons per household I_{kj} varies.

Other parameters in eq.(2) are the probability to progress directly from the susceptible state to the infected state, denoted as ρ; σ, the partial immunity enjoyed by latent and recovered people; and σ_v, the partial immunity enjoyed by vaccinated individuals. Thus one can express the probabilities of exogenous and endogenous active re-infection as $\sigma\rho P_{Inf}$ and $P_{\varpi}=\varpi \times \frac{1}{2 \times 365}$ respectively. Also, the probability to gain a latent re-infection is $\sigma(1-\rho)P_{Inf}$. This latent re-infection term appears in the last column of the 2nd row of L_H (cf. eq.(2)); it is multiplied with the number of recovered persons in the household and adds to the number of latently infected persons.

If the case finding probability is given by *f*, and the probability of successful treatment is δ, then the probability to recover following treatment is:

$$P_{\phi}=\varphi \times f \times \delta \times \frac{1}{2 \times 365}.$$

The treatment rate is φ. For example, a value of φ = 2 per year implies the average time that elapses from the time a person becomes actively infected until treatment is sought, is 6 months. The parameter *f* combines the probability to go to a clinic and the probability that the correct diagnosis is made at the clinic. The probability to recover for latently infected persons is the chemoprophylaxis rate times the activity period:

$$P_{\psi}=\psi \times \frac{1}{2 \times 365}.$$

Recovery without any use of chemical prophylaxis is merely the natural cure rate times the activity period.

$$P_C = c \times \frac{1}{2 \times 365}.$$

Values of the treatment and natural cure rates, φ and *c*, are listed in Table 3.

2.6 Transmissions for commuters during travel

Here we have chosen minibus taxi's as the main mode of transport to model (although buses and trains will have similar effects if the volume and air changes parameters are adjusted accordingly). Frequently, the commuters walk to the nearest main road where there is a steady stream of shared minibus taxis. For the commute model, individuals are randomly assigned to a minibus taxi – in this model the passenger capacity is taken as 10 persons. Taxis are filled to capacity until the number of people who remain unassigned to a taxi is less than ten; the final taxi is populated with this remainder. The operator $L_{commute}$ has the same form as L_H (eq. 2), but $P_{commute}$ is used instead of P_{Inf}. The other values of the operator $L_{commute}$ are not changed from 12 to 2 hours, to account for the continuation of other activities during the 10 hours at work. There is only one mapping per day, since one mapping and a two hour commute gave the same results two mappings of one hour commutes. The time step is therefore the total commuting time per day. The probability for infection in a minibus where *I* of the passengers are infectious is similar to eq. 3:

$$P_{Inf}(I) = 1 - \exp\left[-\frac{rI\gamma}{V_c}\left(\frac{2N_c + \exp[-2N_c] - 1}{N_c^2}\right)\right] \tag{4}$$

Note that the exposure time is six times shorter than in eq. 3 (see Table 1 for activity times) and the volume is sixteen times smaller. The ventilation rate in the vehicle was taken constant at 0.9 air changes per minute, which is nearly ten times higher compared to the home value. This value is based on secondhand smoke inhalation studies (Ott *et al.*, 2008). The ventilation rate could be an important seasonal factor. Note: the unit for ventilation is AC/minute, but for the calculations, the values are scaled to the time of the activity.

The probability $P_{commute}$ depends on the product of $P_{Inf}(I)$ and the probability to have *I* infected passengers in a taxi minibus. The latter probability is determined as follows. If T_w and I_w are the total number of commuters and infected commuters respectively, then the probability to have *I* infected passengers on a minibus, is given by the hypergeometric distribution:

$$P(I) = \frac{\binom{10}{I}\binom{W - I^W}{10 - I}}{\binom{W}{10}}.$$

Therefore the probability to become infected during the commute is

$$P_{commute} = \sum_{I=1}^{9} P(I) \times P_{Inf}(I) \tag{5}$$

Eq. 5 is used in the operator $L_{commute}$.

2.7 Transmission for non-commuters

Random interaction in the community is modeled by calculating the expected number of encounters with an infectious person in the 12-hour period assigned to this activity. The passable area of the community is modeled as a grid divided into 1 m × 1 m squares. An individual occupies one 1 m × 1 m square and moves to an adjacent, un-occupied square after each time step τ. An encounter is defined as an event in which a susceptible, latent, or recovered person occupies a square adjacent to that of an infectious person. Let A be the area of the grid. Assuming that active TB prevalence is relatively low and the grid is relatively large, for each susceptible, latent, and recovered person, the probability of an encounter in a single time step is $4I^U / A$ and the expected number of encounters in the interval $0 \le t \le t_{walk}$ is $4I^U t_{walk}/(A\tau)$. Assume that the probability of encountering two or more infectious persons at once is negligible. Since encounters are relatively rare, assume the number of encounters per person per 12-hour walk is Poisson-distributed. Then the probability for a noninfectious person to have k encounters is

$$P_{encounter}(k) = \frac{\exp\left[-4I^U t_{walk}/(A\tau)\right] \times \left[4I^U t_{walk}/(A\tau)\right]^k}{k!}.$$

The probability for a susceptible person to be infected during the walk is

$$P_{walk} = \sum_k P_{encounter}(k)\left[1 - \exp\left(\frac{-rk\gamma}{V_w}\left[\frac{N_w\tau + \exp[-N_w\tau] - 1}{{N_w}^2}\right]\right)\right]. \quad (6)$$

There are important differences between P_{walk} and the probabilities for infection during the night's rest and the commute: the Poisson distribution that is used in eq. 6 only has a duration of τ minutes, and the total activity time only features in $P_{encounter}$. The operator L_{Day} maps the non-commuting segment of the population onto itself:

$$L_{Day} U_{kj}^n = U_{kj}^{n+1}.$$

The operator L_{Day} has the same form as L_H, but P_{walk} is used instead of P_{Inf}.

To summarize, the model maps, on a daily basis:

$$L_H F_{kj}^n = F_{kj}^{n+1}. \quad \textit{family socializing and rest}$$
$$L_{commute} W_{kj}^n = W_{kj}^{n+1} \quad \textit{commuters during travel}$$
$$L_{Day} U_{kj}^n = U_{kj}^{n+1} \quad \textit{casual intermingling in the township for non-commuters}$$

3. Results and Discussion

The model is applied as described above and intervention parameter values are varied in order to determine the effect of different intervention strategies on the disease outcome over a number of years.

3.1 Effects of family size and daily activities

In this model, the rate of TB transmission (in literature typically referred to as β infections yr^{-1}), is imbedded in the probabilities of acquiring TB infection during the different

activities, given by eqns. 3–6. It is instructive to compare the rate of transmission for the model with values used by other authors. The transmission parameter β is defined as the number of people an infectious person is expected to infect in a year. We have assumed that at the onset of the simulation, the population is 1% infected, 27% susceptible, 67% latent and 5% recovered. The other parameters are listed in Table 2 and 3. If the simulation is run over one year, then $\beta = 17.4\ yr^{-1}$ for commuters, $11.1\ yr^{-1}$ for non-commuters, and $13.0\ yr^{-1}$ for the population as a whole. Our estimated transmission parameters are in agreement with the WHO estimate of 10–15 transmissions per year (WHO TB fact sheet, March 2007).

In Figure 2 the cumulative number of infections is plotted as a function of time (over the span of one year) for six individuals from families of varying size, and according to their commuting status. An infected person from a small family (2 members) that does not commute transmits the fewest new cases, between 2 and 3 infections per year. The daily random walk assumes open air conditions; hence the probability for transmission is lessened. At night only one other person is exposed. On the other hand a person that commutes daily and who comes from a large family (10 members), is responsible for 23 new infections per year. Other cases fall between these two extremes. The difference in transmission rates underscores the importance of type of activity and family size. Other authors (Schinazi (2002),Belhadji and Lanchier (2006)) have identified this dependence on cluster size (household size) and infection rate from outside (which is determined by the activity during the day). However, here we were able to identify how one member of the household can acquire the infection during the commute and introduce the infection to the rest of the household.

To further demonstrate the role of the commute, the fraction of the total population that has active TB is plotted over a twenty year period for two cases: (a) 30% of the population commute daily and (b) 90% of the population commute daily. The other parameters are as listed in Table 2 and 3. The results are shown in Figure 3. The model predicts a near-doubling in the infectious fraction of the population over 20 years if the commuters are increased to 90% of the population. If the commuting fraction drops to 10%, the active infection lowers gradually after peaking at 1.4% at 80 months (results not shown). Our results are in qualitative agreement with a study on the effect of commuting by minibus by Horna-Campos *et al.* (2007). The authors studied the association between commuting by minibuses and pulmonary tuberculosis (TB) for individuals in Lima, Peru and found that traveling in minibuses was a risk factor for pulmonary TB. Of particular interest is their finding that the morning commute coincides with the time expectorant cough is most productive.

3.2 Predicted effects of different intervention strategies

There are several different intervention strategies that can be followed to affect the progression of the disease. The following intervention strategies are simulated: i) vaccination of the susceptible population, ii) physical measures during the commute (e.g. face masks) that reduce the rate of infectious quanta production, iii) prophylactic treatment of latent infection, and iv) increased efficacy in case-finding and treatment of active disease. These interventions are evaluated individually in sections 3.2.1–3.2.4, with a combination of interventions being explored in section 3.2.5.

3.2.1 BCG Vaccination—The BCG vaccination coverage in South Africa was reported to be 76% in 2008 (WHO vaccine-preventable diseases: monitoring system 2009 global summary). However, to simplify calculations here we explore the predicted outcome if the entire susceptible population were to be vaccinated.

Vaccination of the susceptible population is modeled by reduction of the vaccination immunity factor (σ_v) to 0.05, 0.25, 0.5 or 0.75 for 95%, 75%, 50% or 25% protection by vaccination respectively. The value of 50% protection through vaccination corresponds to the results of a meta-analysis by Colditz *et al.* (1994), and is much more conservative than the 75% protection used by Gomes *et al.* (2004). Results are shown in Figure 4A, along with the reference curve ($\sigma_v = 1$).

In this example, a vaccine providing 50% protection of the susceptible population is predicted to slow the increase of infections and contain the prevalence of disease at the current levels for at least ten years. Vaccination is predicted to have a profound effect on the steep increase in cases seen after 4 years in the reference curve. However, a vaccine providing only 25% protection is not predicted to dramatically affect the outcome of the epidemic over 10 years. This result is partly due to the migration strategy employed in this model (i.e. that 1% of the incoming population is infectious). In other words, even though the current population is protected, infectious individuals are constantly entering the population maintaining the infectious levels. However, if a more effective vaccine can be developed and efficiently administered that provides up 75–95% protection against infection, a significant decrease in prevalence is predicted by the model. A halving of prevalence is predicted for a 95% effective vaccine, over ten years.

3.2.2 Physical measures—Another point of intervention is the quanta production by infectious individuals. The use of standard surgical face masks (either by infectious individuals or susceptible individuals) as a way of reducing the inhalation of infectious particles is a cumbersome intervention, but still a useful one. It has recently been more widely employed in the wake of the H1N1 influenza pandemic. The intervention modeled here is not exclusively representative of the use of face masks, but rather it is taken to envelop any behavioral/physical means of lowering the release of infectious particles by infectious persons into the environment.

The behavioral intervention is integrated into the model by a lowering of the parameter γ by 25%, 50% or 95% for commuters during their travel. Nicas (1995) found surgical masks provide a 50% reduction in cumulative risk of infection, while N95 respirators are predicted to filter 99% of bacteria of similar shape and size to *Mycobacterium tuberculosis* (Qian *et al.*, 1998). The choice of 25% reduction is a conservative estimate, to account for non-compliance by part of the population, while the 95% reduction is an exploration of a “best case scenario”.

Results are shown in Figure 4B. A 25% reduction in quanta production only slightly reduced the infected fraction, but did seem to have an effect on the rate of decrease in prevalence after the eight year mark. An intervention resulting in 95% reduction in quanta production is predicted to contain the infectious levels at current levels for at least 10 years. A 50% reduction in quanta production has a predicted outcome between these two extremes. Although, the effects of behavioral changes do not appear to be very significant, they are encouraging when considering that they are only applied to the small subpopulation (30%) that commute daily, and only for 2 hours out of every day. When considering the impact family size is predicted to have on transmission of disease (see Figure 2), one could also consider behavioral changes that allow the protection of family members during the most infectious stages of the disease.

3.2.3 Prophylactic treatment of latent TB infection—The diagnosis and treatment of latent infections is extremely difficult, but nonetheless an important step that needs to be considered in disease control.

The prophylactic treatment of latent tuberculosis is represented, in this model, by the parameter ψ. An increase in either the finding or treatment of latent cases is simulated by an increase in the value of ψ (from 0.1 to 0.25, 0.5, 1 and 2 per year).

Results are shown in Figure 4C. Prophylactic treatment of latent TB is predicted to result in a much lower increase in disease at four years, followed by a much faster decrease in disease after six years. However, most of the benefits are seen in the increase between 0.1 and 1 per year, with little improvement when diagnosis frequencies are simulated to be 2 per year.

Diagnosing latent infection is very difficult since it is asymptomatic. The effects of this intervention will be bigger when considering an HIV^+ population, since the reactivation rate (ω) is much higher, compared to HIV^- individuals.

3.2.4 Increased case-finding and treatment of active disease—Perhaps the most obvious route of intervention is an increase in the correct diagnosis and effective treatment of active cases of tuberculosis. Diagnosis delay and inappropriate therapy has been said to facilitate transmission and development of drug resistance in highly HIV co-infected populations in South Africa (Calver *et al.*, 2010). The factors determining recovery following treatment in this model constitute the case-finding rate (*f*), rate of treatment (φ) and treatment success rate (δ). Since these factors are all multiplied in the probability of recovery (P_φ), changes in the different parameters will all have a similar effect.

Changes in treatment is simulated by changing the rate of treatment parameter (φ) to 1.5, 2 and 3 $year^{-1}$. Note: the different factors determining recovery is explored in more detail in the next section.

Results are shown in Figure 4D. Increased rate of treatment is by far the most effective individual intervention in the control of the disease (compare Figure 4A–C). The infected fraction of the population is predicted to decrease almost immediately and sharply, and for treatments rates of 2 and higher, followed by a long term steady decline in disease burden. A case finding rate of 3 per year is predicted to reduce prevalence by 80% over ten years. It should be noted that this strategy is one of the six components of the WHO Stop TB strategy (The Stop TB Strategy, 2006).

3.3 Combination of approaches

Finally, a multifaceted approach comprising interventions at multiple points in the progression of the epidemic is simulated by combining the approaches outlined in the sections above.

Results are shown in Figure 5. The reference curve is the same result that is also in Figures 3 and 4 for 30% commuters and parameter values as given in Tables 2 and 3. Representative curves from each of the interventions are shown, along with a curve simulating the combined effect of all of these interventions. The behavioral intervention curve depicts the change in the fraction of infectious persons if masks or scarves are used to reduce the infectious quanta production by 25%, for the commuter population. The vaccination curve represents the predicted outcome if the susceptible population is vaccinated and obtains a 50% protection against productive infection. The treatment frequency curve predicts the outcome if treatment frequencies are increased to 2 $year^{-1}$. Finally, the prophylactic latency treatment curve predicts the outcome over ten years if latent infection can be treated at 0.5 $year^{-1}$. The combination curve represents the predicted effects if all of these intervention strategies are implemented at once.

The combination approach is predicted to be the most effective strategy for disease control in these high burden communities, resulting in a sharp decline in the infectious fraction, and near eradication within ten years.

An interesting observation becomes evident if the intervention strategies are considered in the context of Figure 1: the behavioral, vaccination and latent prophylaxis strategies all reduce the rates of flow into the infectious sub-population, but case-finding and treatment is the only strategy that increases the rate of flow out of that sub-population. From the results in Section 3.2 it follows that, for this population, interventions that speed the flow of individuals out of the infectious pool (increase case finding and treatment) is more effective than those interventions that prevent entry of individuals into the infectious pool (e.g. behavioral changes and vaccination). Therefore, in the next section, we further discuss the different factors that affect recovery.

3.4 Factors that affect recovery

The probability to recover following treatment is the product of several other probabilities. These conditions are the case finding probability and correct diagnosis, bundled as *f*, the probability of successful treatment δ, the treatment frequency φ, and the treatment period:

$$P_{\phi}=f \times \delta \times \varphi \times t_{activity}.$$

The treatment frequency φ (with units of year^{-1}) is multiplied by the activity period to find the probability that treatment will be sought during the interval $t_{activity}$. For example, a value of φ = 2 year^{-1} implies that there is an average delay of six months before treatment is sought.

The probabilities *f* and $\varphi \times t_{activity}$ are arguably not independent; if the delay time becomes short, then the patient may not yet produce sputum, and clinical specimens are paucibacillary in all likelihood. Thus *f* should approach true case finding probability when diagnostic sensitivity approaches 100% at long delay times (small values of φ) and *f* should become zero when delay times are too short to produce enough CFU per sputum sample.

Remark: The delay time to seek treatment must not be confused with the processing time for the diagnostic procedure. New diagnostic methods are developed and turn-around times have been drastically reduced, however these advanced technologies are not yet the standard of care. Hence the delay times for smear microscopy and culture studies are still the norm.

In Figure 6 the combined effect of $\varphi \times f$ on TB deaths over a ten year period is shown. Let $f = 0.5$ be a case finding maximum; to a large extent this maximum is a result of the very low percentage of HIV positive persons who become infected with TB but do not seek treatment. Further, assume that the diagnostic technology is so advanced that 100% sensitivity is achieved, even for smear negative cases that are presented 3 months after infection. Thence a delay time of $\varphi^{-1} = 1$ year results in nearly 2,000 deaths over a ten year period. If the delay time drops to 6 months, the total number of deaths is 850. At 4 and 3 month delay times, the total number of deaths is 480 and 320 respectively. But Figure 5 lends itself to other interpretations. If the diagnostic sensitivity is only 80% for smear negative cases and the 3rd month after infection is the soonest a person becomes sputum productive, then the maximum value of $\varphi \times f = 4 \times 0.5 \times 0.8 = 1.6$. In this case, the total deaths after ten years is 440, which still marks a near five-fold reduction in mortality, compared to the case $\varphi \times f = 0.5$.

Figure 7 (reproduced from "Diagnostics for tuberculosis: global demand and market potential" (Special Programme for Research and Training in Tropical Diseases 2006)) represents the typical timeline of a person since active infection. Two striking observations can be made from this graph, if it is brought into context with Figure 6. The patient first visits the clinic after 2 months, but remains un-diagnosed. The acid-fast bacilli (AFB) smear negative test that is administered after the 3rd month also does not lead to a diagnosis. Thus patients voluntarily present themselves at clinics 2 to 3 months after infection. Furthermore, the patient is typically diagnosed after the 5th month as the result of a positive AFB test. At 5 months, and an assumed sensitivity of 90% for the AFB test at this point in time, $\varphi \times f = (12/5) \times 0.5 \times 0.9 = 1.08$, which places close to the green curve in Figure 5. It becomes apparent from this brief discussion that, even within the constraint of limited case finding, significant gains can be made if the diagnostic technology becomes so sensitive to diagnose smear negative clinical specimens at the 3 month mark and the cost of the test is so low that authorities can implement the test at clinics, even for smear negative cases.

4. Conclusions

Mathematical models are valuable tools in analyzing the dynamics of the spread of disease, and informing intervention strategies. Some valuable insights into the spread of disease in an informal settlement have been gathered from the model presented here. The main conclusions are summarized below.

- Epidemiological models that consider the whole population under one average set of parameters may overlook some very important transmission dynamics in the different subpopulations.
- Clustering a population on more than one level can elucidate important disease dynamics of different daily activities.
- Members of larger families are responsible for more disease transmissions than those from smaller families, mostly during interactions in the home.
- A daily commute in a minibus taxi provides ideal conditions (many people in a small space for a prolonged period) for the spread of disease. Even if the commuter population is a minority, interventions in this part of the population can have a profound impact.
- An increase in the efficacy of diagnosis and treatment has the greatest impact on the spread of disease, when compared to vaccinations, behavioral changes or treatment of latent infections. Not that the latter three interventions should be overlooked.
- Increased sensitivity of diagnostic tests will allow earlier diagnosis of disease upon the patients' first visit to the clinic (see Figures 6 and 7).
- Diagnostic tests must be affordable to allow more widespread implementation of screening.
- Ultimately, the eradication of this global burden will require intervention on as many fronts as possible, with increased focus on the most infectious subpopulations.

5. Future Directions

The model described here can be expanded to distribute the infectious population (I) as a function of time since infection, thus including the disease dynamics outlined in Figure 7

above. Further expansions are also possible to include HIV status, gender and age and updated parameter values.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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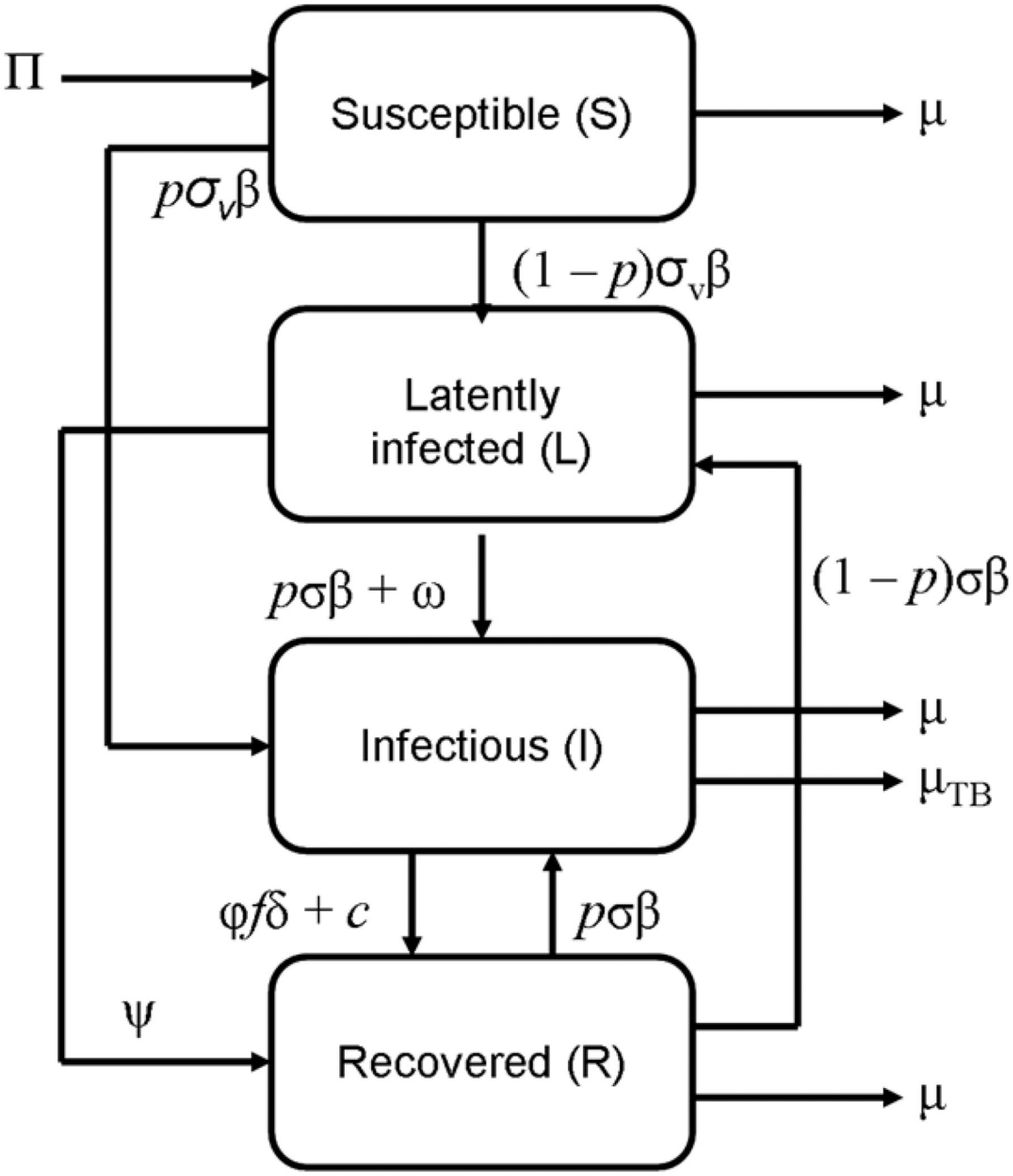

Figure 1.
A flowchart of TB exposure. The parameters are defined in Tables 2 and 3. For clarity, the commuting and non-commuting subpopulations are not distinguished here. It is important to note that the value of β is determined by a combination of several different social interactions.

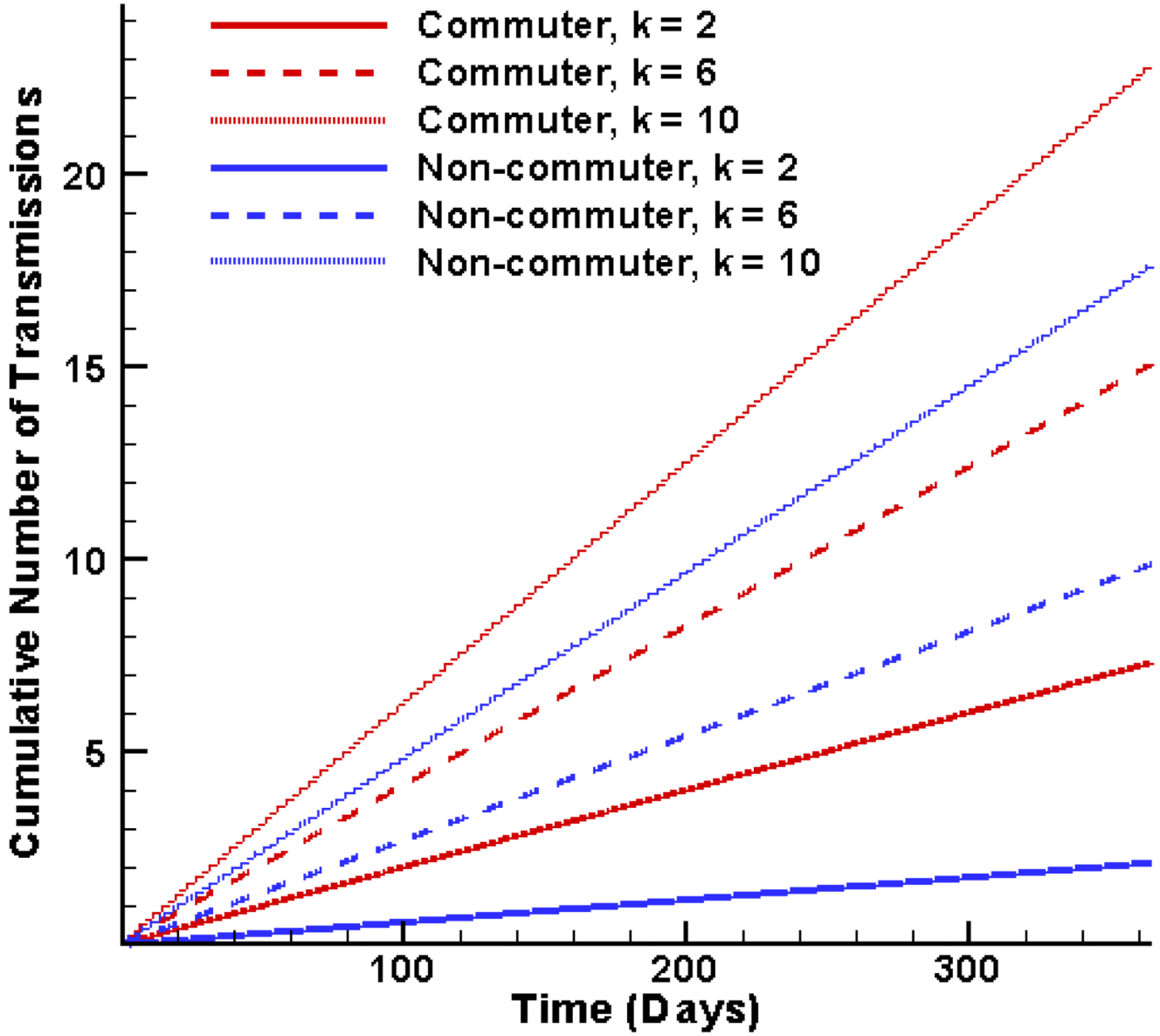

Figure 2.
Number of persons infected by commuters and non-commuters from different family sizes as a function of time.

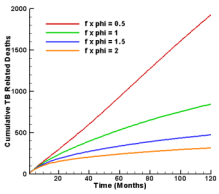

Figure 3.
Changes in the total infectious fraction of the population infection over a period of 20 years for (a) 30% daily commuting (red curve) and (b) 90% daily commuting (green curve).

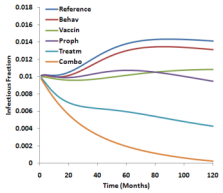

Figure 4.

(A) Predicted effects of different levels of protection (25–95%) from vaccination, compared to the reference curve (no protection). (B) Predicted effects of different levels of protection (25–95%) from behavioral changes, compared to the reference curve (no behavioral changes). (C) Predicted effects of different frequencies (0.25–2 per year) of prophylactic treatment of latent infections, compared to the reference curve (0.1 per year). (D) Predicted effects of different frequencies (1.5–3 per year) of treatment of active disease, compared to the reference curve (1 per year).

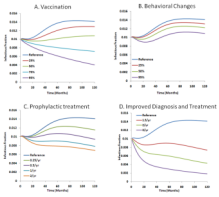

Figure 5.

Predicted outcome for the infectious fraction of the population under representative intervention strategies. (Reference): Reference curve for 30% commuters. (Behav): Behavioral interventions. (Vaccin): Vaccination of susceptible population. (Proph): Prophylactic treatment of latent infections. (Treatm): Increased frequency of treatment of infectious individuals. (Combo): Combination of all other interventions depicted. Further details about the curves are given in the text.

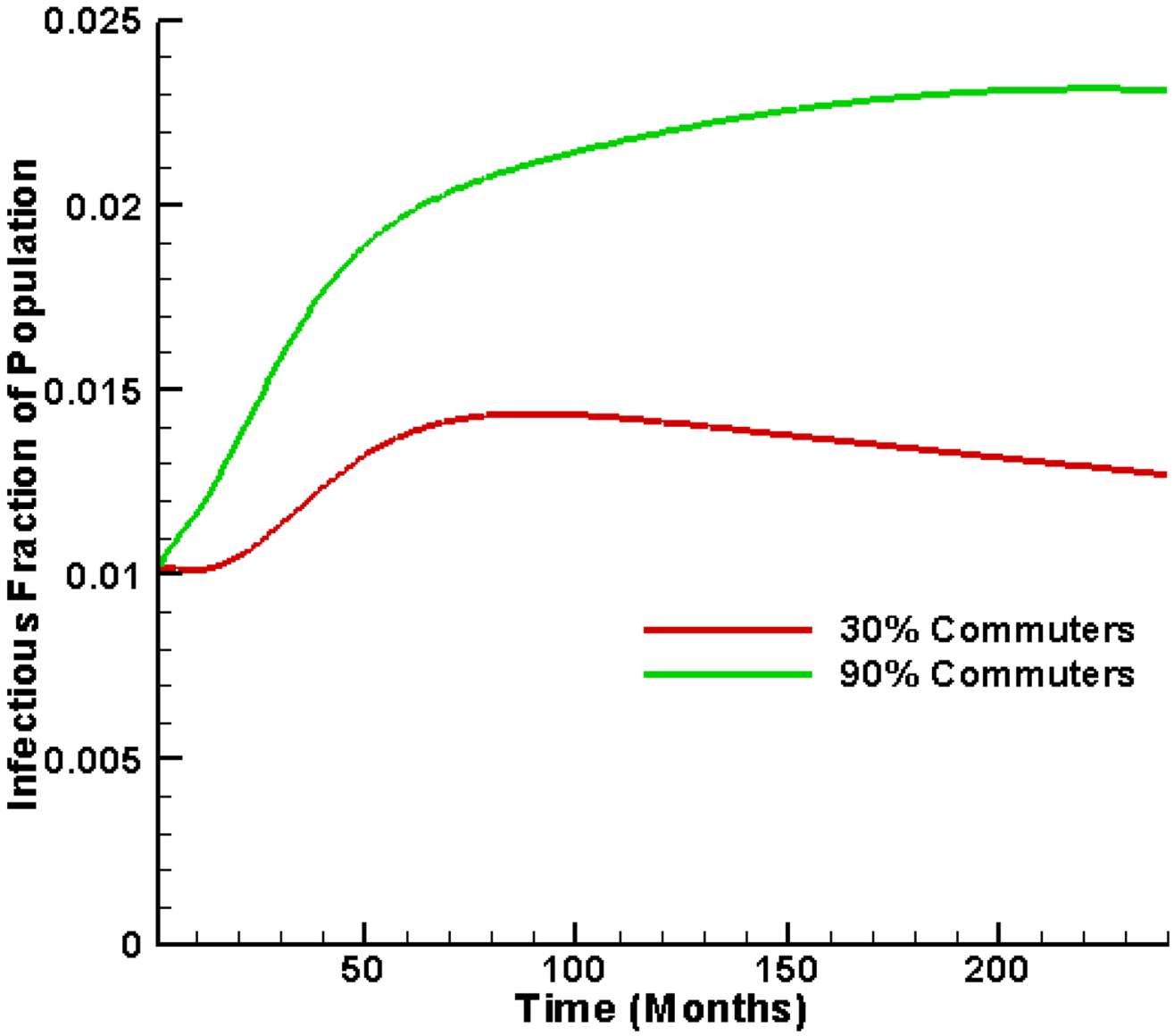

Figure 6.
Cumulative TB related deaths over 10 years, in a township with constant population, with φ^{-1} = 1 year (red), 6 months (green), 4 months (blue) and 3 months (orange) and f = 0.50, ε = 0.30.

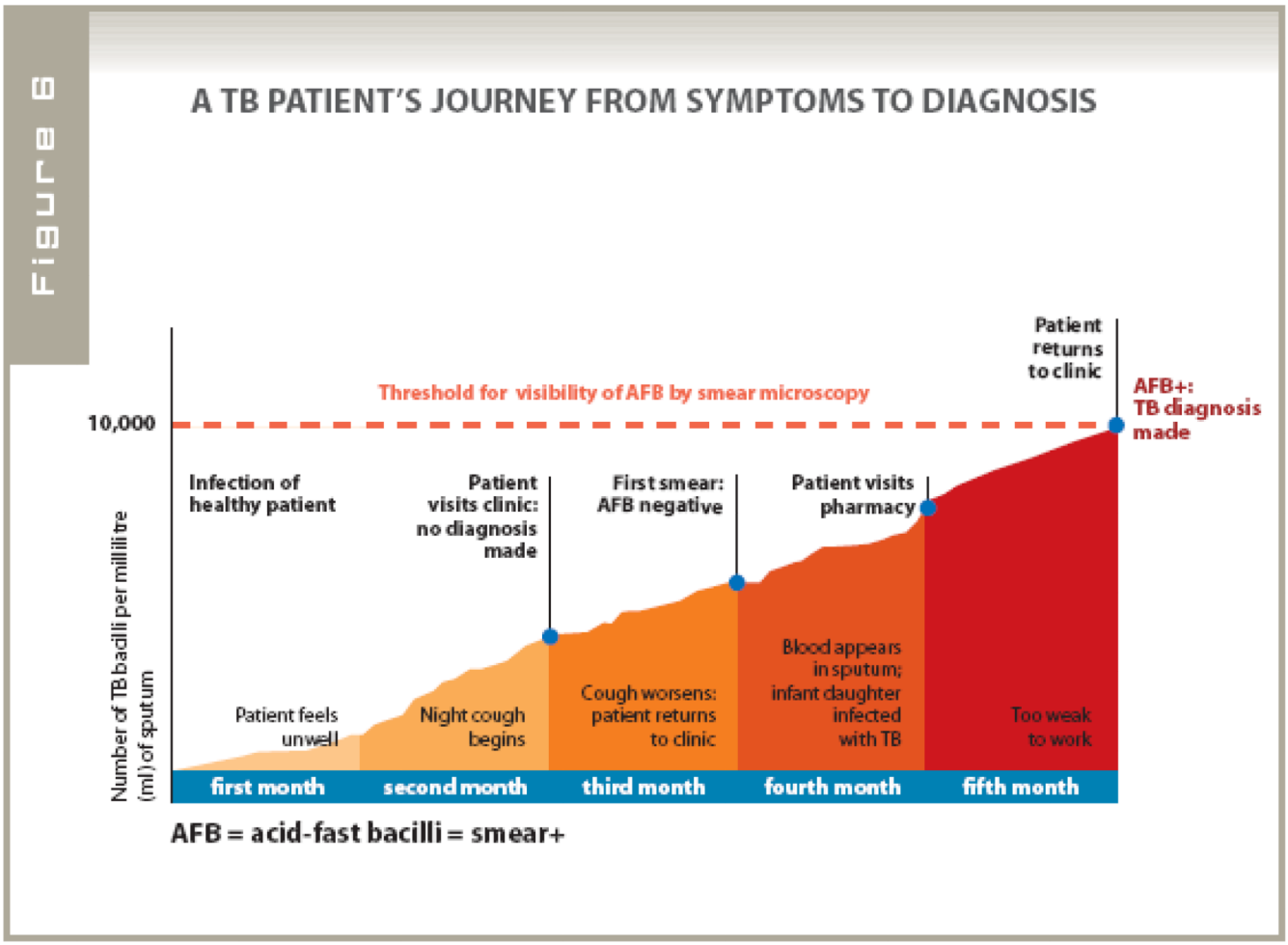

Figure 7.

Timeline of an infected person with active TB. Reproduced from "Diagnostics for tuberculosis: global demand and market potential" (Special Programme for Research and Training in Tropical Diseases 2006).

Table 1

Daily schedule

Duration (hr)	Commuter activity	Non-commuter activity
12	Sleep/interact at home	Sleep/interact at home
1	Morning commute	Random walk Interact in community
10	Daily interaction	
1	Afternoon commute	

Table 2

Daily schedule

Duration (hr)	Commuter activity	Non-commuter activity
12	Sleep/interact at home	Sleep/interact at home
1	Morning commute	Random walk Interact in community
10	Daily interaction	
1	Afternoon commute	

Table 3

Other model parameters

Symbol	Parameter	Value	Unit	Reference
ε	Employed fraction of total population	0.30		Mears (1997)
π	Birth rate	0.0293	$year^{-1}$	van Rie et al. (1999)
μ	Death rate from non-TB causes	0.0134	$year^{-1}$	Anderson & Phillips (2006), WHO (2009)
μ_{TB}	Death rate from active TB	0.333	$year^{-1}$	
ρ	Proportion of infectious cases with fast progression to active TB	0.05		Gomes et al. (2004)
ω	Rate of endogenous reactivation	0.00256	$year^{-1}$	Blower & Gerberding (1998)
σ	Factor of partial immunity	0.25		Gomes et al. (2004)
σ_v	Factor of partial immunity due to vaccination	1		Gomes et al. (2004)
Ψ	Rate of chemoprophylaxis of latent individuals	0.10	$year^{-1}$	Blower & Gerberding (1998)
φ	Rate of treatment of infectious individuals	1.0	$year^{-1}$	Wood et al. (2007)
f	Standard case-finding proportion	0.40		Wood et al. (2007)
δ	Treatment success rate	0.74		WHO (2009)
c	Natural cure rate	0.058	$year^{-1}$	Blower et al. (1995)